

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re New Divisional U.S. Patent Application of:)	
)	
Applicant:	Henry B. Kopf)	Docket No.: 2780-105 DIV2
)	
Application No.:	Not Assigned)	
)	
Prior App. No.:	09/397,291)	
)	
Date Filed:	April 9, 2001)	
)	
Title:	CULTURE DEVICE AND METHOD)	
)	

EXPRESS MAIL CERTIFICATE

I hereby certify that I am mailing the attached documents to the Commissioner for Patents on the date specified, in an envelope addressed to the Commissioner for Patents, Washington, D.C., 20231 and Express Mailed under the provisions of 37 CFR 1.10.

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April 9, 2001

Date

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PRELIMINARY AMENDMENT

Commissioner for Patents
Box Patent Application
Washington, DC 20231

Sir:

Please amend the enclosed application as follows:

In the Specification:

At page 1, beginning at line 2, immediately following "BACKGROUND OF THE INVENTION," insert the following:

CROSS-REFERENCE TO RELATED APPLICATIONS:

This is a divisional of U.S. Patent Application No. 09/397,291 filed September 15, 1999, issued April 10, 2001 as U.S. Patent 6,214,574, which is a divisional of U.S. Patent Application No. 09/307,932 filed May 10, 1999, which in turn is a continuation of U.S. Patent Application No. 07/207,655 filed June 21, 1988, which in turn is a continuation-in-part of U.S. Patent Application No. 06/936,486 filed November 26, 1986 and now issued as U.S. Patent 4,885,087.

In the Claims:

Please cancel claims 1-19, and add the following new claims 20-84:

20. A tangential-flow filter for selectively transferring a species from a fluid mixture to a fluid media, the filter comprising:
 - a. a filtration membrane having a first surface and a second surface;
 - b. a cassette formed with a first channel and a second channel, the first channel having an input port and an output port being disposed to establish a tangential flow of the fluid mixture over the first surface of the membrane, the second channel having an input port

and an output port being disposed to establish a tangential flow of the fluid media over the second surface of the membrane; and

- c. means for creating a pressure differential between the fluid mixture in the first channel and the fluid media in the second channel to cause the species to traverse the membrane from the fluid mixture to the fluid media.
21. The tangential-flow filter of claim 20 wherein the first channel and the second channel are positioned side-by-side.
22. The tangential-flow filter of claim 20 wherein the first channel and the second channel are positioned coaxially.
23. The tangential-flow filter of claim 20 wherein the filtration membrane is chosen to selectively pass species having a molecular weight of approximately 1 to 1000 kDa.
24. A cell culture device for in vitro cell population growth, the cell growth occurring in fluid growth media within the device, the device comprising:
- a. a first hollow fiber cartridge having a housing and a plurality of capillaries, each of the capillaries including walls having interiors and exteriors, the housing having a first inflow opening and a first outflow opening, the plurality of capillaries extending between the first inflow opening and the first outflow opening, at least one of the capillaries having selectively permeable walls, the interiors of the walls of the plurality of capillaries defining a first lumen extending between and being in fluid communication with the first inflow opening and the first outflow opening, the exteriors of the walls of the plurality of capillaries and the housing defining a first extracapillary space, the housing having a first primary orifice in fluid communication with the first extracapillary space;
 - b. a second hollow fiber cartridge having a housing and a plurality of capillaries, each of the capillaries including walls having interiors and exteriors, the housing having a second inflow opening and a second outflow opening, the plurality of capillaries extending between the second inflow opening and the second outflow opening, at least one of the capillaries having selectively permeable walls, the interiors of the walls of the plurality of capillaries defining a second lumen extending between and being in fluid communication

with the second inflow opening and the second outflow opening, the exteriors of the walls of the plurality of capillaries and the housing defining a second extracapillary space, the housing having a second primary orifice in fluid communication with the second extracapillary space; and

- c. a fluid connecting mechanism for fluidly connecting the first and second cartridges, the fluid connecting mechanism including a recirculation mechanism for recirculating fluid media from the respective outflow openings of the hollow fiber cartridges to inflow openings thereof and an extracapillary space connecting mechanism for fluidly connecting the first extracapillary space with the second extracapillary space, the recirculation mechanism including a mechanism for providing oxygen to the media.

25. A cell growing device for in vitro cell population growth, the cell growth occurring in fluid growth media within the device, the device comprising:

- a. a plurality of first hollow fiber cartridges, each of the plurality of first hollow cartridges having a housing and a plurality of capillaries, each of the capillaries including walls having interiors and exteriors, the housing having a first inflow opening and a first outflow opening, the plurality of capillaries extending between the first inflow opening and the first outflow opening, at least one of the capillaries having selectively permeable walls, the interiors of the walls of the plurality of capillaries defining a first lumen extending between and being in fluid communication with the first inflow opening and the first outflow opening, the exteriors of the walls of the plurality of capillaries and the housing defining a first extracapillary space, the housing having a first primary orifice in fluid communication with the first extracapillary space;
- b. a plurality of second hollow fiber cartridges, each of the plurality of second hollow cartridges having a housing and a plurality of capillaries, each of the capillaries including walls having interiors and exteriors, the housing having a second inflow opening and a second outflow opening, the plurality of capillaries extending between the second inflow opening and the second outflow opening, at least one of the capillaries having selectively permeable walls, the interiors of the walls of the plurality of capillaries defining a first lumen extending between and being in fluid communication with the second inflow opening and the second outflow opening, the exteriors of the walls of the plurality of

- capillaries and the housing defining a second extracapillary space, the housing having a second primary orifice in fluid communication with the second extracapillary space;
- c. a fluid connecting mechanism for fluidly connecting the plurality of first cartridges with the plurality of second cartridges, the first cartridges being connected in parallel and the second cartridges being connected in parallel, the fluid connecting mechanism including a recirculation mechanism for recirculating fluid media from the respective outflow openings of the hollow fiber cartridges to inflow openings thereof and extracapillary space connecting mechanism for fluidly connecting the extracapillary spaces of the plurality of first cartridges with those of the plurality of second cartridges; and
 - d. a valve mechanism for controlling the flow of fluid media through the fluid connecting mechanism, the valve mechanism including a switch mechanism for selectively switching the flow of media between alternate fluid pathways.
26. A cell growing device for in vitro cell population growth, the cell growth occurring in fluid growth media within the device, the device comprising:
- a. a first hollow fiber cartridge having a housing and a plurality of capillaries, each of the capillaries including walls having interiors and exteriors, the housing having a first inflow opening and a first outflow opening, the plurality of capillaries extending between the first inflow opening and the first outflow opening, at least one of the capillaries having selectively permeable walls, the interiors of the walls of the plurality of capillaries defining a first lumen extending between and being in fluid communication with the first inflow opening and the first outflow opening, the exteriors of the walls of the plurality of capillaries and the housing defining a first extracapillary space, the housing having a first primary orifice in fluid communication with the first extracapillary space;
 - b. a second hollow fiber cartridge having a housing and a plurality of capillaries, each of the capillaries including walls having interiors and exteriors, the housing having a second inflow opening and a second outflow opening, the plurality of capillaries extending between the second inflow opening and the second outflow opening, at least one of the capillaries having selectively permeable walls, the interiors of the walls of the plurality of capillaries defining a second lumen extending between and being in fluid communication with the second inflow opening and the second outflow opening, the exteriors of the

walls of the plurality of capillaries and the housing defining a second extracapillary space, the housing having a second primary orifice in fluid communication with the second extracapillary space; and

- c. a fluid connecting mechanism for fluidly connecting the first and second cartridges, the fluid connecting mechanism including a recirculation mechanism for recirculating fluid media from the respective outflow openings of the hollow fiber cartridges to inflow openings thereof and an extracapillary space connecting mechanism for fluidly connecting the first extracapillary space with the second extracapillary space.
27. The cell growing device of claim 26, wherein the device further includes a monitoring mechanism for monitoring and adjusting the oxygen concentration and the pH of the media located in the first extracapillary space.
28. The cell growing device of claim 27, wherein the extracapillary space monitoring mechanism includes a gas transfer mechanism.
29. The cell growing device of claim 26, wherein the selectively permeable walls have a molecular weight cut-off of equal to or less than about 30,000 daltons.
30. A cell culture system comprising:
- a. a plurality of cell culture chambers each comprising cells in a culture medium;
 - b. a gas-liquid exchange device;
 - c. a conduit system to conduct culture medium between said gas-liquid exchange device and said plurality of cell culture chambers;
 - d. a circulation mechanism for circulating culture medium through said conduit system, said plurality of cell culture chambers, and said gas-liquid exchange device, including circulating culture medium between said plurality of cell culture chambers.
31. A method for culturing cells, the method comprising:
- a. providing cell culturing system comprising:

- i. a plurality of cell culture chambers;
 - ii. a gas-liquid exchange device;
 - iii. a conduit system to conduct culture medium between said gas-liquid exchange device and said plurality of cell culture chambers; and
 - iv. a circulation mechanism for circulating culture medium through said conduit system; and
 - b. circulating the culture medium through said plurality of cell culture chambers, said gas-liquid exchange device, and said conduit system with said circulation mechanism.
32. A method for culturing cells, the method comprising:
- a. placing a source of cells into a perfusable cell culture device said device comprising:
 - i. two liquid impermeable polymeric film sheets constructed so as to deliver oxygen and carbon dioxide at rates sufficient to maintain cells in culture joined together at their peripheral edges in a sealing manner, one of the sheets defined as an upper polymeric layer and the other defined as a lower polymeric layer;
 - ii. a gas and liquid permeable flow divider membrane affixed between said upper polymeric layer and said lower polymer layer and affixed to said lower polymeric layer so as to provide channels for fluid distribution with a pressure drop across the flow divider membrane;
 - iii. an inlet port in said lower polymeric layer through which culture medium can be introduced between said lower polymeric layer and said flow divider membrane;
 - iv. said upper polymeric layer and said flow divider membrane being arranged with respect to each other so as to form a chamber between said upper polymeric layer and said flow divider membrane through which growth medium can be perfused across the surface of the flow divider membrane and in which cells are cultured; and

- v. a port in said upper polymeric layer through which cells may be placed into the cell culture device, cultured cells may be removed from said cell culture device, and perfused nutrients may be collected from said cell culture device;
 - b. perfusing said device with a cell culture medium; and
 - c. withdrawing spent culture medium through said port in the upper polymeric layer.
33. A cell propagation system comprising:
- a. at least two hollow fiber bioreactors each of said bioreactors comprising:
 - i. a casing;
 - ii. hollow fibers positioned in said casing;
 - iii. an extracapillary space defined by the interior surface of said casing and the exterior surfaces of said hollow fibers;
 - iv. a first inlet means for fluid flow into the lumens of said hollow fibers;
 - v. a second inlet means for fluid flow into said extracapillary space;
 - vi. said second inlet means further comprising valve means for the control of fluid separately through said extracapillary space of each of said bioreactors;
 - vii. a first outlet means for withdrawal of fluid from the lumens of said hollow fibers;
 - viii. a second outlet means for withdrawal of fluid from said intracapillary space;
 - b. a fluid flow path connecting said first inlet and said first outlet means of each of said bioreactors; and
 - c. a fluid flow path connecting said second inlet means and said second outlet means of each of said bioreactors.

34. The cell propagation system of claim 33 further comprising means for providing a controlled fluid flow rate through said fluid flow path connecting said second inlet means and said second outlet means of each of said bioreactors.
35. The cell propagation system of claim 33 further comprising means for introduction of nutrients into said fluid flow path.
36. A hollow fiber cell culture system comprising:
- a. at least two hollow fiber bioreactors including nutrient permeable hollow fibers positioned in an extracapillary space of said bioreactors;
 - b. a loop for flowing fluids through lumens of said fibers, said loop comprising:
 - i. pump means for circulating fluids through said loop;
 - ii. means for introducing gases into said loop;
 - iii. means for determining and controlling the temperature of said fluids;
 - iv. means for determining and controlling the dissolved oxygen content of said fluids upstream or downstream of said bioreactors;
 - v. means for controlling the flow rate of said fluids through said loop;
 - vi. means for controlling pH of said fluids;
 - vii. means for introducing fluids comprising said nutrient into said loop; and
 - c. means for flowing fluids through said extracapillary spaces.
37. A method for culturing cells, the method comprising:
- a. inoculating extracapillary space of at least two hollow fiber bioreactors with cells;
 - b. circulating medium comprising a nutrient into and through lumens of hollow fibers of said bioreactors;

- c. introducing oxygen into said circulating medium to establish and maintain an oxygen content sufficient to support metabolism of said cells.
38. A hollow fiber cell propagation system comprising:
- a. at least two hollow fiber bioreactors each of said bioreactors comprising:
 - i. a casing,
 - ii. hollow fibers positioned within said casing, and
 - iii. an extracapillary space defined by the interior surface of said casing and the exterior surfaces of said hollow fibers,
 - b. a first fluid flow loop connected to first inlet means and to first outlet means to provide flow of fluids through the lumens of said hollow fibers,
 - c. a fluid flow path connected to second inlet means and second outlet means to provide flow of fluids through said extracapillary space.
39. A cell culture device comprising:
- a. a first casing that defines a cell growth chamber configured to carry a quantity of biological cells and growth media;
 - b. a source of growth medium connected to the cell growth chamber;
 - c. a port connected to the cell growth chamber configured to carry media discharged from the growth chamber;
- wherein the cell growth chamber, the source of growth medium, and port are connected together to form a closed system configured to be sterilizable as a unit; and
- d. a flow control device for transporting growth media through the cell growth chamber, from the from the source of growth medium and through the exit port without exposing the closed, sterile system to the external environment;

wherein the cell growth chamber is configured to be inoculated with biological cells, and thereafter to maintain and grow the inoculated biological cells while the flow control device transports growth media through the cell growth chamber, from the from the source of growth medium and through the exit port without exposing the closed, sterile system to the external environment.

40. A cell culture device comprising;
- a. a housing;
 - b. a cell culture space within said housing;
 - c. fresh nutrient medium inlet and outlet means, connected, in parallel, to tubes contacting said culture space;
 - d. gas supply means for supplying metabolic gas to the cell culture space;
 - e. a spent medium outlet means;

wherein said tubes in connection with fresh nutrient medium inlet and outlet means, which are structured in a closed-loop circuit, are constructed so as to provide a supply of fresh medium through said tubes.

41. A filtration cassette comprising a multilaminate array of sheet members of generally rectangular and generally planar shape with main top and bottom surfaces, wherein:
- a. the sheet members include in sequence in the array:
 - i. a first retentate sheet;
 - ii. a first filter sheet;
 - iii. one or more permeate sheets;
 - iv. a second filter sheet; and
 - v. a second retentate sheet;

- b. each of the sheet members in the array has at least one inlet basin opening at one end thereof, and at least one outlet basin opening at an opposite end thereof, with at least one permeate passage opening;
 - c. each of the first and second retentate sheets has at least one channel opening therein, wherein each channel opening extends longitudinally between the inlet and outlet basin openings of the sheets in the array and is open through the entire thickness of the retentate sheet; and
 - d. each of the first and second retentate sheets is sealed to an adjacent filter sheet about peripheral end and side portions thereof, with their basin openings and permeate passage openings in register with one another, and arranged to permit flow of filtrate through the channel openings of the retentate sheet between the inlet and outlet basin openings to permit permeate flow through the filter sheet to the one or more permeate sheets to the permeate passage openings;
 - e. the filtration cassette comprises a unitary article of inter-bonded sheet members.
42. A filtration cassette according to claim 41, wherein the permeate passage opening constitutes at least one permeate passage opening on each of two side margin portions of the sheet members.
43. A filtration cassette according to claim 41, wherein the permeate passage opening constitutes at least one permeate passage opening on each of the two longitudinal side margin portions of the sheet members
44. A filtration cassette according to claim 43, wherein the permeate passage opening constitutes multiple openings at the longitudinal side margin portion of each said sheet.
45. A filtration cassette according to claim 44, wherein the permeate passage openings at each longitudinal side margin portion of each said sheet are longitudinally aligned with one another.
46. A filtration cassette according to any one of claims 42, 43, 44 and 45, further comprising two permeate material egress ports in fluid communication with said permeate passage openings at side margin portions of the sheet members, wherein a second fluid can pass through the permeate sheet from one permeate egress port to the second.

47. A filtration cassette according to any one of claims 41, 42, 43, 44, 45 and 46, wherein the permeate sheet is of rigid character.
48. A filtration cassette according to any one of claims 41, 42, 43, 44, 45 and 46, wherein the one or more permeate sheets are of screen or mesh construction.
49. A filtration cassette according to any one of claims 41, 42, 43, 44, 45 and 46, wherein the sheet members are inter-bonded by a bonding technique selecting from the group consisting of heat bonding, ultrasonic bonding, radio frequency bonding, and microwave bonding.
50. A filtration cassette according to any one of claims 41, 42, 43, 44, 45 and 46, wherein at least two sheet members of the cassette are at least in part microwave bonded to one another.
51. A filtration cassette according to any of claims 41, 42, 43, 44, 45 and 46, wherein inlet and outlet basin openings are devoid of sharp corners.
52. A filtration cassette according to any of claims 41, 42, 43, 44, 45 and 46, wherein filter sheets are bonded to respective faces of the one or more permeate sheets, with a weld line interior to the basin openings, and with adhesive bonding interior to the weld lines.
53. A filtration cassette according to claim 52, wherein said weld line is formed by radio frequency welding or ultrasonic welding.
54. A stacked cassette filter including a stacked assembly of filtration cassettes, wherein:
 - a. each filtration cassette comprises a multilaminate array of sheet members of generally rectangular and generally planar shape with main top and bottom surfaces;
 - b. the sheet members include in sequence in the array:
 - i. a first retentate sheet;
 - ii. a first filter sheet;
 - iii. one or more permeate sheets;
 - iv. a second filter sheet; and

- v. a second retentate sheet;
 - c. each of the sheet members in the array has at least one inlet basin opening at one end thereof, and at least one outlet basin opening at an opposite end thereof, with at least one permeate discharge opening;
 - d. each of the first and second retentate sheets has at least one channel opening therein, wherein each channel opening extends longitudinally between the inlet and outlet basin openings of the sheets in the array and is open through the entire thickness of the retentate sheet;
 - e. each of the first and second retentate sheets is sealed to an adjacent filter sheet about peripheral and side portions thereof, with their basin openings and permeate passage openings and register with one another, and arranged to permit flow of filtrate through the channel openings of the retentate sheet between the inlet and outlet basin openings to permit permeate flow through the filter sheet to the one or more permeate sheets to the permeate passage openings;
 - f. the filtration cassette comprises a unitary article of inter-bonded sheet members.
55. A filtration cassette according to claim 54, wherein the permeate passage opening constitutes at least one permeate passage opening on each of two side margin portions of the sheet members.
56. A filtration cassette according to claim 54, wherein the permeate passage opening constitutes at least one permeate passage opening on each of the two longitudinal side margin portions of the sheet members.
57. A filtration cassette according to claim 56, wherein the permeate passage opening constitutes multiple openings at the longitudinal side margin portion of each said sheet.
58. A filtration cassette according to claim 57, wherein the permeate passage openings at each longitudinal side margin portion of each said sheet are longitudinally aligned with one another.
59. A filtration cassette according to any one of claims 55, 56, 57 and 58, further comprising two permeate material egress ports in fluid communication with said permeate passage openings at

- side margin portions of the sheet members, wherein a second fluid can pass through the permeate sheet from one permeate egress port to the second.
60. A stacked cassette filter according to any one of claims 54, 55, 56, 57, 58 and 59, wherein an outermost filtration cassette comprises an outermost retentate sheet of rigid character.
61. A stacked cassette filter according to claim 60, wherein an outermost filtration cassette comprises a retentate sheet bonded to an endplate to provide a hard shell cassette structure, and the endplate is positioned adjacent a manifold plate of the filter with a compressible gasket between the endplate and the manifold plate.
62. A filtration cassette comprising a multilaminate array of sheet members of generally rectangular and generally planar shape with main top and bottom surfaces, wherein:
- a. the sheet members include in sequence in said array:
 - i. a first retentate sheet;
 - ii. a first filter sheet;
 - iii. one or more permeate sheets;
 - iv. a second filter sheet; and
 - v. a second retentate sheet;
 - b. each of the sheet members in said array has at least one inlet basin opening at one end thereof, and at least one outlet basin opening at an opposite end thereof, with at least one permeate passage opening;
 - c. each of the first and second retentate sheets has at least one channel opening therein, wherein each channel opening extends longitudinally between the inlet and outlet basin openings of the sheets in the array and is open through the entire thickness of the retentate sheet, and with each of the first and second retentate sheets being bonded to an adjacent filter sheet about peripheral end and side portions thereof, with their basin openings and permeate passage openings in register with one another and the filtrate

passage openings of each of the retentate sheets being circumscribingly compression bonded to the adjacent filter sheet;

- d. a central portion of each of the retentate sheets and adjacent filter sheets is unbonded to permit permeate contacting the retentate sheet to flow through the filter sheet to the one or more permeate sheets; and
 - e. each of the filter sheets is secured at its peripheral portions on a face thereof opposite the retentate sheet, to a permeate sheet.
63. A filtration cassette according to claim 62, wherein the permeate passage opening constitutes at least one permeate passage opening on each of two side margin portions of the sheet members.
64. A filtration cassette according to claim 62, wherein the permeate passage opening constitutes at least one permeate passage opening on each of the two longitudinal side margin portions of the sheet members.
65. A filtration cassette according to claim 64, wherein the permeate passage opening constitutes multiple openings at the longitudinal side margin portion of each said sheet.
66. A filtration cassette according to claim 65, wherein the permeate passage openings at each longitudinal side margin portion of each said sheet are longitudinally aligned with one another.
67. A filtration cassette according to any one of claims 63, 64, 65 and 66, further comprising two permeate material egress ports in fluid communication with said permeate passage openings at side margin portions of the sheet members, wherein a second fluid can pass through the permeate sheet from one permeate egress port to the second.
68. A filtration cassette according to any one of claims 41, 54 and 62, wherein each of the one or more permeate sheets and retentate sheets comprises a woven polymeric mesh.
69. A filtration cassette according to claim 68, wherein the woven polymeric mesh comprises a material selected from the group consisting of polyester, polypropylene, nylon, fluorocarbon polymers, polyethylene, and polysulfone.

70. A filtration cassette according to any one of claims 41, 54 and 62, wherein each of the retentate sheets have a thickness between 0.125 mm and 6.0 mm.
71. A filtration cassette according to any one of claims 41, 54 and 62, wherein each of retentate sheets is formed of a material selected from the group consisting of polysulfone, polyether sulfone, polyetherimide, polycarbonate, silicone, urethane.
72. A filtration cassette according to any one of claims 41, 54 and 62, wherein the filter sheets comprise a material selected from the group consisting of cellulose, polyphenylene oxide, polysulfone, cellulose nitrate, cellulose acetate, polyether amide, polyphenylene oxide/polysulfone blends, mixed esters of cellulose, regenerated cellulose, nylon, polyvinylidene fluoride, and polyethersulfone.
73. A filtration cassette according to any one of claims 41, 54 and 62, wherein the array of sheet members comprises a non-compressible retentate sheet including a series of transversely spaced-apart, longitudinally extending ribs, each extending outwardly from the plane of the sheet to an outer extremity, with filter sheets bonded to the non-compressible retentate sheet.
74. A filtration cassette according to claim 73, wherein the longitudinally extending ribs are formed of an adhesive bonding material.
75. A filtration cassette according to claim 74, wherein the adhesive bonding material comprises a material selected from the group consisting of urethane, epoxy, cyanoacrylate, and silicone adhesives.
76. A filtration cassette according to any one of claims 41, 54 and 62, wherein the sheets in the cassette are bonded to one another with an adhesive bonding medium comprising a material selected from the group consisting of urethane, epoxy, cyanoacrylate, and silicone adhesives.
77. A filtration cassette according to any one of claims 41, 54 and 62, further comprising a feed material inlet port communicating with said at least one inlet basin opening, and a retentate outlet port communicating with said at least one outlet basin opening, with one of said inlet and outlet ports being on one of said main top and bottom surfaces, and the other of said inlet and outlet ports being on the other of said main top and bottom surfaces.

78. A filtration cassette according to any one of claims 41, 54 and 62, further comprising a feed material inlet port communicating with said at least one inlet basin opening, and a retentate outlet port communicating with said at least one outlet basin opening, wherein the inlet and outlet ports are diagonally opposite one another on said cassette.
79. A stacked cassette filter including a stacked assembly of filtration cassettes each comprising a multilaminate array of sheet members of generally rectangular and generally planar shape with main top and bottom surfaces, wherein:
- a. each filtration cassette comprises a multilaminate array of sheet members of generally rectangular and generally planar shape with main top and bottom surfaces;
 - b. the sheet members include in sequence in said array:
 - i. a first retentate sheet,
 - ii. a first filter sheet,
 - iii. one or more permeate sheets,
 - iv. a second filter sheet, and
 - v. a second retentate sheet;
 - c. each of the sheet members in said array has at least one inlet basin opening at one end thereof, and at least one outlet basin opening at an opposite end thereof, with permeate passage openings at longitudinal side margin portions of the sheet members;
 - d. each of the first and second retentate sheets has at least one channel opening therein, wherein each channel opening extends longitudinally between the inlet and outlet basin openings of the sheets in the array and is open through the entire thickness of the retentate sheet;
 - e. each of the first and second retentate sheets is bonded to an adjacent filter sheet about peripheral end and side portions thereof, with their basin openings and permeate passage openings in register with one another and the filtrate passage openings of each of the

retentate sheets being circumscribingly compression bonded to the adjacent filter sheet, and with a central portion of each of the retentate sheets and adjacent filter sheets being unbonded to permit permeate contacting the retentate sheet to flow through the filter sheet to the one or more permeate sheets; and

- f. each of the filter sheets is secured at its peripheral portions on a face thereof opposite the retentate sheet, to the one or more permeate sheets.
80. A stacked cassette filter including a stacked assembly of filtration cassettes each comprising a multilaminate array of sheet members of generally rectangular and generally planar shape with main top and bottom surfaces, wherein:
- a. each filtration cassette comprises a multilaminate array of sheet members of generally rectangular and generally planar shape with main top and bottom surfaces;
 - b. the sheet members include in sequence in said array:
 - i. a first retentate sheet,
 - ii. a first filter sheet,
 - iii. one or more permeate sheets,
 - iv. a second filter sheet, and
 - v. a second retentate sheet;
 - c. each of the sheet members in said array has at least one inlet basin opening at one end thereof, and at least one outlet basin opening at an opposite end thereof, with at least one permeate passage opening;
 - d. each of the first and second retentate sheets has at least one channel opening therein, wherein each channel opening extends longitudinally between the inlet and outlet basin openings of the sheets in the array and is open through the entire thickness of the retentate sheet;

- e. each of the first and second retentate sheets is bonded to an adjacent filter sheet about peripheral end and side portions thereof, with their basin openings and permeate passage openings in register with one another and the filtrate passage openings of each of the retentate sheets being circumscribingly compression bonded to the adjacent filter sheet, and with a central portion of each of the retentate sheets and adjacent filter sheets being unbonded to permit permeate contacting the retentate sheet to flow through the filter sheet to the one or more permeate sheets; and
 - f. each of the filter sheets is secured at its peripheral portions on a face thereof opposite the retentate sheet, to the one or more permeate sheets.
81. A filtration cassette according to claim 80, further comprising a feed material inlet port in communication with said inlet basin openings and a retentate outlet port in communication with said outlet basin openings, wherein the inlet and outlet ports are on opposite sides of the stacked sheet members.
82. A filtration cassette according to any one of claims 80 and 81, further comprising a feed material inlet port in communication with said inlet basin openings and a retentate outlet port in communication with said outlet basin openings, wherein the inlet and outlet ports are diagonally opposite one another in relation to the sequence of stacked sheet members.
83. A process for effecting mass transfer between a liquid growth medium and a liquid medium containing biological species, in a membrane growth device including a membrane, the process comprising circulating one of the liquid media through at least one membrane growth device, on one side of the membrane, and simultaneously circulating a second one of said liquid media inoculated with a cell culture through said membrane growth device on an opposite side of said membrane from said first liquid medium.
84. A method of culturing cells, comprising:
- a. providing a tangential flow membrane device;
 - b. providing a culture fluid in loop fluid communication with the tangential flow membrane device;

- c. flowing culture fluid through the tangential flow membrane device on a first side of a membrane thereof;
- d. discharging a fluid from the tangential flow membrane device from a second side of said membrane thereof;
- e. monitoring the culture fluid for at least one process parameter, and responsively inoculating the culture fluid with a microorganism, and/or adding one or more supplements to enable growth of said microorganism, wherein said supplement(s) comprises at least one of oxygen, culture media, acids, bases, buffers and cellular nutrients.

REMARKS

Claims 1-19 have been cancelled herein, and new claims 20-84 have been added.

A set of formal drawings for the application is enclosed, in replacement for the informal drawings enclosed with the true and exact copy of the specification, since the informal drawings were originally filed in the parent application, and their presence is therefore required.

Likewise, a true and exact copy of the Declaration and Power of Attorney from the parent application is enclosed, together with a new Declaration specifically executed for this divisional patent application by the inventor.

Please initiate examination of the application on the basis of claims 20-84 now pending and constituting the claims of the application.

Respectfully submitted.



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**INTELLECTUAL PROPERTY/
TECHNOLOGY LAW**

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